

NATIONAL INSTITUTES OF HEALTH
FISCAL YEAR 2005
PLAN FOR HIV-RELATED RESEARCH

III: THERAPEUTICS

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH
OFFICE OF AIDS RESEARCH

AREA OF EMPHASIS:

Therapeutics

SCIENTIFIC ISSUES

Scientific advances resulting from basic research on the viral life cycle, pathogenic mechanisms, and host-virus relationship continue to provide a strong foundation for the design, development, and evaluation of improved treatment regimens for HIV infection and its associated co-infections, opportunistic infections, and malignancies. The NIH supports a comprehensive AIDS therapeutics research program with the goal of developing new and better approaches to prevent, treat, and control HIV infection and its sequelae. The use of antiretroviral therapy (ART) continues to result in the significant reduction of viral load, increased CD4 cell counts, decreased opportunistic infections (OIs), and improved immune function in patients who are able to adhere to the treatment regimens and tolerate the toxicities associated with the antiretroviral (ARV) drugs.

A high priority of NIH AIDS therapeutics research continues to be the development of better drugs and therapeutic regimens that are less toxic and have fewer side effects, limit the development of drug resistance, enter viral reservoirs to inhibit viral replication, promote easier adherence, and are more readily accessible. The global impact and continued spread of the AIDS pandemic in both developed and developing nations underscore the urgent need to develop therapeutic regimens that can be properly implemented in international settings.

The scientific agenda for NIH AIDS therapeutics research is focused upon answering the following questions:

- Are there new viral and cellular targets against which therapies can be directed?
- What therapeutic agents and regimens can be developed that target drug-resistant virus and have activity in viral compartments and cellular reservoirs?
- What are the optimal therapeutic approaches for management of HIV infection, including when to start, change, sequence, or interrupt therapy?
- How can the pharmacologic and toxicologic properties of these agents be improved?
- What are the pharmacokinetics of these drugs in pregnant and breastfeeding women, and what impact does this have upon the fetus?
- What are the immunologic determinants to predict the efficacy of immune-based therapies?
- What is the impact of co-infection upon disease progression and treatment of both HIV and the co-existing infection, such as hepatitis B virus (HBV), hepatitis C virus (HCV), tuberculosis (TB), or malaria?
- What are the clinical and public health ramifications of ART treatment in developing countries?
- What types of interventions facilitate the delivery of therapeutic interventions for HIV disease in a resource-poor setting?

**PRECLINICAL
DEVELOPMENT OF
NEW THERAPEUTIC
AGENTS**

PRIORITIES FOR FUTURE RESEARCH:

- **Advance the discovery and validation of new viral and cellular targets.**
- **Develop new therapeutic agents that:**
 - ▶ **target drug-resistant virus;**
 - ▶ **have activity in viral reservoirs and cellular compartments; and**
 - ▶ **have improved pharmacologic and toxicologic properties.**

The NIH sponsors an active and comprehensive drug discovery and development program that permits the design and identification of new, safe, and more effective drugs and drug regimens that target drug-resistant virus, have activity in viral reservoirs and cellular compartments, and have improved pharmacologic and toxicologic properties. The discovery and validation of new viral and cellular targets is key to the development of next generation and better therapeutic agents and regimens. Collaborations between Government, academia, and industry are essential to ensure continued advances in AIDS drug development research, preclinical development of new agents, and clinical trials. The goal of these programs is to develop therapeutic agents and regimens that slow disease progression, extend life expectancy, and improve the quality of life for HIV-infected individuals in both developed and developing countries.

NIH-sponsored programs provide resources for conducting preclinical testing of potential compounds against HIV infection and its sequelae. Evaluation of the biological properties of these drugs, as well as their pharmacology and toxicology, in model systems permits a better understanding of their potential role in the treatment armamentarium. The importance of these models is further emphasized by the increasing role of drug toxicities and complications in causing significant morbidity and mortality. Additional efforts are essential to accelerate the development and testing of microbicides and of other chemical and physical barriers to halt the sexual transmission of HIV and other sexually transmitted diseases (STDs). A separate component of this Plan has been developed for this critical area of NIH-sponsored research. Collaborations between Government-sponsored programs and the pharmaceutical and biotechnology industries are essential in advancing potential microbicidal agents through the drug development process.

CLINICAL EVALUATION OF THERAPIES

PRIORITIES FOR FUTURE RESEARCH:

- **Determine optimal therapeutic strategies including when to start (early versus late), change, sequence, or interrupt therapies and evaluate therapeutic drug monitoring strategies.**
- **Identify regimens with improved toxicity, efficacy, pharmacokinetics, activity in viral reservoirs, adherence potential, and reduced cost.**
- **Target affected populations, especially women, injecting drug users (IDUs), children, adolescents, older adults, and across racial/ethnic groups. Conduct studies that permit evaluation of potential differences in response to therapy due to gender and/or racial/ethnic differences.**

- **Enhance capabilities for long-term followup and evaluate the long-term effects of therapy and the implications of these findings on public health.**
- **Conduct studies to evaluate the implications of therapy to prevent HIV transmission on public health.**
- **Identify immunologic correlates of effective viral suppression in the setting of clinical therapeutic intervention trials.**

The widespread use of ART in HIV patient care has resulted in increased life expectancy and improved quality of life for many HIV-infected individuals in the United States and Western Europe since 1996. Sharp declines in AIDS death rates and substantial reductions in the incidence of AIDS-related OIs beginning with the use of ART have continued through 2001. Initial sharp declines in new AIDS cases observed in 1996 have leveled off and remained the same since 1999. Unfortunately, a growing proportion of HIV-infected individuals receiving therapy experience treatment failure with ART failing to reduce viral loads. Some patients are unable to comply with complex treatment regimens, experience toxicities and side effects, or cannot afford their high cost. An increase in side effects and complications leading to liver failure, kidney disease, and cardiovascular disease has been observed as HIV-infected individuals continue on drug regimens. One of the highest priorities of NIH-sponsored AIDS research continues to be the clinical evaluation of potential agents and the development of treatment regimens against HIV infection and its associated OIs and malignancies. Clinical research targets the identification of better drugs and treatment regimens to reduce and overcome these limitations, so that HIV-infected individuals can live longer with improved quality of life and delayed disease progression.

The AIDS epidemic in the United States continues to affect diverse communities including women, racial and ethnic minorities, adolescents, substance and alcohol abusers, and older adults. The NIH continues to place a high priority on the recruitment and retention of individuals from these affected populations in clinical trials to the extent that they reflect the ongoing epidemic. Increased enrollment of these communities may permit evaluation of potential differences in response to therapy due to gender and/or racial and ethnic differences.

Clinical trials permit the identification of safe and effective treatment regimens with increased efficacy, decreased toxicity, improved pharmacokinetics, activity in viral reservoirs, and easier adherence. The metabolic and morphologic complications associated with these treatment regimens present

significant morbidity and mortality, thus warranting further investigation. These studies also will help define when to begin, switch, and interrupt drugs within treatment regimens and identify therapies for treatment-experienced individuals who no longer respond to the ARVs that are currently available. Clinical findings from NIH-sponsored studies are continuing to provide crucial information leading to better treatment regimens for HIV-infected individuals. The translation of clinical trial results into treatment guidelines and standards of care that can be used by health care providers is critical in bringing results from the “bench to the bedside” and, ultimately, resulting in better care for those affected by HIV disease.

MOTHER-TO-CHILD TRANSMISSION INTERVENTION

PRIORITIES FOR FUTURE RESEARCH:

- **Develop safe, effective, feasible, and conveniently administered strategies to interrupt mother-to-child transmission (MTCT) of HIV. Focus on international studies to inhibit MTCT with special emphasis on breastfeeding.**
- **Evaluate the safety and pharmacokinetics of antiretroviral agents in pregnant and breastfeeding women, including studies on the transplacental passage of the agents and safety for the fetus.**
- **Evaluate pharmacokinetics, metabolism, tissue absorption, and drug elimination in the newborn.**
- **Conduct studies to evaluate and reduce short- and long-term toxicity of ARVs to prevent HIV transmission in women during pregnancy, and in their offspring who were perinatally exposed.**

The NIH has placed a priority on the continued development and testing of interventions to halt MTCT of HIV, especially treatment regimens that can be implemented in developing nations. While there has been success in the United States and many developed nations, MTCT continues to be a significant problem in developing countries and resource-poor settings, particularly settings where breastfeeding is prevalent and replacement feeding is not feasible. A better understanding is needed of the mechanisms, timing, and risk factors for breast milk transmission. Further progress is needed to identify better treatment approaches that can block MTCT, including transmission associated with breastfeeding. In addition, a better understanding is needed of the short- and long-term effects of these interventions upon the fetus and the mother.

Significant advances have been made in the prevention of MTCT since the success of the Pediatric AIDS Clinical Trials Group (PACTG) protocol 076. Widespread implementation of the PACTG 076 regimen in the United

States and Western Europe has resulted in a mother-to-child transmission rate of less than 2 percent. Clinical studies are underway to answer many of the remaining scientific questions about the treatment of HIV infection during pregnancy. Some of these studies focus on: safety and pharmacokinetics of antiviral agents in pregnant and breastfeeding women and neonates; transplacental and breast milk passage of these agents; development of drug resistance; and potential short- and long-term effects of these ARVs on the mother and child.

The development and testing of safe, effective, affordable, and sustainable interventions to inhibit MTCT that can be used in resource-limited settings is a priority. The implementation of effective regimens remains a challenge in resource-limited settings and in settings where women are diagnosed late in pregnancy or postpartum in developed nations. The widespread use of ARVs in these settings is further complicated by a complex array of challenges including co-infections and endemic diseases, limited availability of health care staff and facilities, and limited capabilities for clinical and laboratory monitoring. Innovative approaches are needed to define and implement effective regimens among such populations.

EVALUATION OF CO-INFECTION

PRIORITIES FOR FUTURE RESEARCH:

- **Evaluate the effects of co-infection, especially with HBV, HCV, TB, or malaria, on the management of HIV. Determine the bidirectional effects of co-infection and treatments on disease progression and drug interactions.**
- **Develop new agents for the treatment of HBV, HCV, TB, and malaria in the setting of HIV infection, with specific attention to pharmacologic drug interactions and nonoverlapping toxicity.**

HCV infection is continuing to spread at an alarming rate in the United States, as well as globally. The continued expansion of the AIDS epidemic in this country into substance abuse and minority communities translates into greater numbers of co-infected individuals. The NIH continues to place a priority on the development and evaluation of potential therapies for the prevention and treatment of HIV-associated infections and co-infections. A better understanding is needed to determine the bidirectional effects of co-infection and treatments for these co-infections on disease progression and drug interactions. In international settings, hepatitis, TB, and malaria continue to play significant roles as comorbidities of HIV infection. New and better drugs and therapeutic regimens are needed for the treatment of HBV, HCV, TB, and malaria as co-infections of HIV infection, with particular attention to drug-drug interactions and minimizing toxicities.

DEVELOPMENT OF IMMUNE-BASED THERAPEUTICS

PRIORITIES FOR FUTURE RESEARCH:

- **Develop and evaluate therapeutic approaches including vaccines that will improve and sustain immune function or prevent transmission of HIV infection.**
- **Identify and validate immunologic determinants to predict the efficacy of immune-based therapies.**

Recent studies continue to provide important insights into the pathogenesis of HIV infection and the role of individual immune factors in containing the infection. While the initiation of ART has afforded improvements with restoration of immune function and improved immunologic parameters, further study is needed to determine what therapeutic approaches can improve and sustain immune function. The development of immunologic therapeutic approaches that can prevent transmission of HIV infection from infected individuals to uninfected individuals is important. Similarly, the identification of immunologic determinants that will predict the efficacy of immune-based therapies is needed.

INTERNATIONAL

PRIORITIES FOR FUTURE RESEARCH:

- **Expand international clinical research programs in countries with limited resources.**
- **Design and conduct clinical studies that are appropriate for diverse international settings.**
- **Design studies to improve and facilitate the delivery of therapeutic and prevention interventions for HIV disease.**
- **Evaluate the clinical and public health impact of antiretroviral treatment.**
- **Evaluate the clinical and public health impact of prophylactic and therapeutic interventions for co-infections/OIs.**
- **Encourage studies that integrate therapeutic regimens and prevention interventions.**

The NIH has placed a high priority on the conduct of international AIDS research and the development of drug regimens to prevent, treat, and control HIV disease and its co-infections in developed and developing nations. These studies require the direct involvement of host nation researchers as equal partners in the design, conduct, and analysis of clinical trial protocols. This approach ensures the involvement of the host nation in the conduct of the clinical study, as well as the implementation

of therapeutic interventions after the study is completed. Two separate components of this Plan have been developed to address these relevant areas of NIH-sponsored research: Training, Infrastructure, and Capacity Building, and International Research. The increasing urgency of the AIDS pandemic requires that treatment be viewed in the context of other complex and complicating factors: availability of health care resources; trained personnel and infrastructure to provide therapies; co-existing infections; and public health impact. While this represents a significant and daunting challenge, the development of safe, efficacious, sustainable, and affordable treatment regimens must be targeted to all who are affected by HIV disease.

SCIENTIFIC OBJECTIVES AND STRATEGIES

OBJECTIVE - A:

Identify and validate viral and cellular functions required for HIV replication that can be targeted for viral inhibition, clearance, and prevention of transmission. Discover and develop novel agents and therapeutic strategies directed against viral and host factors involved in HIV transmission, infection, replication, and persistence.

(The scientific objectives of A and B are of equal weight.)

STRATEGIES:

- Identify, characterize, and validate new and understudied viral and host targets for anti-HIV therapy (e.g., factors involved in viral fusion, entry, integration, transcription, replication, assembly, budding, infectivity, virulence, and pathogenicity). Develop predictive test models, including appropriate lentivirus animal models, to aid in identifying agents and strategies active against these targets.
 - ▶ Develop agents (including natural products) and treatment strategies that target, inhibit, and clear HIV in cellular, anatomical, and organ reservoirs and sanctuaries.
 - ▶ Characterize potential agents, including their preclinical, immunologic, pharmacokinetic, pharmacodynamic, toxicity, and teratogenicity profiles.
 - ▶ Develop new compounds and chemical formulations, including microbicides and other methods, suitable for the genitourinary and gastrointestinal tracts.
 - ▶ Employ whole animal and *ex vivo* organ or tissue models of lentivirus infections to study the biologic and pharmacologic characteristics of therapeutic agents.
- Acquire structural information on HIV and cell constituents involved in HIV infection for the design of potent therapeutic agents with activity against drug-resistant strains. Post lead structures on publicly accessible databases in real time.
 - ▶ Integrate genomics and informatics paradigms, concepts, and methodologies (microchip-based screens and analyzers) into mainstream drug discovery and development of therapeutic entities and strategies.

- ▶ Develop enabling technologies to accelerate and optimize the discovery and development of therapeutic entities and strategies; establish the infrastructure to provide services and reagents needed by the scientific community.
- ▶ Evaluate the intracellular pharmacokinetics and activity of antiretroviral agents in different cell types, different stages of the cell cycle, and in all age groups. Correlate intracellular pharmacokinetic parameters with drug efficacy/toxicity.
- ▶ Develop agents with desirable biopharmaceutical characteristics (e.g., improved bioavailability and tissue penetration to the central nervous system [CNS] and other sanctuaries); develop drug delivery devices or systems that improve the pharmacokinetic profile of therapeutic agents, target specific organs or tissues, reduce toxicities and adverse effects, and result in improved adherence to therapeutic regimens.
- Study the mechanisms and implications of drug resistance and viral fitness; evaluate early markers and genotypic mutations that lead to resistance and cross-resistance.
 - ▶ Advance basic and applied gene-based strategies to treat HIV infection and its complications. Foster new approaches and technologies to optimize gene delivery that results in regulated and persistent gene expression. Optimize *ex vivo* gene delivery and advance new concepts, strategies, and vectors for direct *in vivo* delivery.
 - ▶ Develop mathematical and computer models of HIV infection and therapeutic interventions that stimulate and predict *in vivo* efficacy, toxicity, and other outcomes of drug regimens and clinical trials. Investigate the use of pharmacogenetics in identifying optimum therapies.
 - ▶ Investigate the host cell effects of antiretroviral drugs.

OBJECTIVE - B:

Conduct clinical trials (including the development of new methodologies) in domestic and international settings, especially in resource developing nations, to: (1) evaluate the short- and long-term safety, efficacy, and effectiveness of therapeutic agents and strategies against HIV infection and transmission; (2) identify optimal and appropriate treatment modalities in treatment-naïve and treatment-experienced HIV-infected individuals; and (3) define, evaluate, and mitigate factors that adversely affect the success of therapeutic strategies against HIV infection. Encourage clinical trial designs that build on epidemiologic studies that advance the understanding of disease pathogenesis and progression. Develop domestic and international partnerships to design and conduct clinical studies.

(The scientific objectives of A and B are of equal weight.)

STRATEGIES:

Clinical Trials of Therapeutic Agents

- Conduct clinical trials of potential therapeutic agents and combinations of agents in adults, adolescents, and children to determine pharmacokinetics, tissue bioavailability, antiviral activity, effects on the immune system, safety, and clinical efficacy.
 - ▶ Evaluate optimal combinations of agents selected for antiviral synergy, complementary mechanism of action, minimal toxicity and cross-resistance, simplicity of administration, and tolerability.
 - ▶ Evaluate optimal therapies and strategies for individuals who have acute or recent infection, chronic infection but no prior antiretroviral therapy, and those with prior antiretroviral therapy including individuals with multiple drug-resistant virus.
 - ▶ Support clinical trials to study:
 - long-term efficacy (including toxicities) of therapeutic strategies;
 - timing, selection, and strategic sequencing of antiretroviral agents to optimize clinical outcome; and
 - effects of structured treatment interruption on virologic, immunologic, and clinical outcome.
 - ▶ Evaluate novel therapeutic modalities (e.g., cell-based, gene-based, and therapeutic vaccine approaches) with state-of-the-art antiretroviral therapies.

- ▶ Evaluate co-formulated antiretrovirals.
- ▶ Evaluate the benefits or risks of commonly used complementary agents (herbal, homeopathic, and/or naturopathic) when used concomitantly with ART.

Clinical Trials Enrollment

- Strengthen efforts and implement new approaches to ensure the enrollment and retention of women, adolescents, minorities, IDUs, and older adults in clinical trials.
- Strengthen efforts to evaluate new and existing drug treatment regimens in clinical trials that reflect the demographics of the epidemic, including traditionally underrepresented populations. When appropriate, evaluate potential gender, race, ethnicity, age-specific, and pregnancy-related differences in drug efficacy and safety, including pharmacokinetics, metabolism, tissue absorption, and drug elimination.
 - ▶ Identify and evaluate the viral and host factors, including human genomics, associated with antiretroviral treatment failure including malabsorption, drug interactions, drug resistance, drug toxicities, pharmacogenetics, and suboptimal adherence.

Clinical Trial Methodology

- Develop and evaluate standardized virologic, immunologic, and clinical markers to assess drug activity; determine and validate the prognostic value of surrogate markers in response to various therapeutic interventions.
- Design, test, and evaluate methods to improve the retention of individuals in clinical trials.
- Develop, incorporate, and validate appropriate quality-of-life parameters in clinical trials of antiretroviral agents.
- Develop methodology to facilitate cross-protocol analysis and meta-analyses.
- Develop methodology for research on the ethical conduct of clinical trials.

Pharmacology

- Determine the relationship between drug exposure (pharmacokinetics) and outcomes (antiviral effect, immune function, and safety) to facilitate dosing strategies within clinical trials, as well as for individual patient management.
- Investigate drug interactions among commonly used treatments for HIV-related disease and its complications, as well as other substances that may be used by HIV-infected individuals.

Viral Reservoirs

- Evaluate the presence and persistence of HIV in different tissue compartments during ART; investigate the role of anatomic and cellular sanctuaries in the development of HIV drug resistance, transmission, and establishment of long-term reservoirs.
- Evaluate the penetration of ARVs into different tissue compartments (e.g., genital secretions/semen, CNS, breast milk, etc.).

Viral Resistance and Fitness

- Explore the utility of real-time antiretroviral phenotypic and genotypic assays in managing ART across a broad spectrum of individuals.
- Evaluate the impact of transmission of drug-resistant HIV strains on disease progression and therapy.

Adherence

- Support research on the effectiveness of pharmacological approaches, behavioral interventions, and other approaches to facilitate better adherence to antiretroviral regimens.
- Develop better methods to assess adherence to treatment regimens across a variety of affected populations; compare and validate adherence measures in the context of HIV treatment.

Co-infection with Hepatitis B Virus and/or Hepatitis C Virus

- Evaluate the bidirectional effects of co-infection with HBV and/or HCV in HIV-infected individuals. Evaluate the impact of ART on reactivation of hepatitis viruses, treatment of viral hepatitis in co-infected individuals, transmission of hepatitis viruses, and development of late-stage complications of viral hepatitis.

International

- Enhance the development of international collaborations that will assist in addressing relevant therapeutic research in populations of HIV-infected adults, adolescents, and children.
- Assist developing nations, as appropriate, in technology transfer through training, infrastructure, and capacity building to facilitate the evaluation of antiretroviral agents and other therapies in local settings.
- Assess the barriers to delivery of effective HIV/AIDS health care including treatment and the capability of conducting international therapeutic clinical trials through the establishment or expansion of multidisciplinary clinical centers.
- Develop and evaluate simpler, reliable, user-friendly, and inexpensive assay technologies for monitoring immunologic and virologic status and antiretroviral drug responses that can be used in resource-poor settings.
- Develop standardized clinical indicators to determine when to initiate ART, to monitor response to therapy, and to determine when to change therapy.
- Evaluate other simple and inexpensive surrogate markers of immunologic and virologic responses for use in resource-poor settings.
- Determine acceptable laboratory monitoring for drug toxicity in resource-poor settings.
- Evaluate the efficacy of ART in HIV-infected women following receipt of antiretroviral prophylaxis to prevent MTCT, including the effect of antiretroviral drug resistance mutations that may arise following prophylaxis on the efficacy of subsequent therapy.
- Evaluate the efficacy of ART in infants/children who become infected despite maternal/infant receipt of antiretroviral prophylaxis to prevent MTCT, including the effects of antiretroviral drug resistance mutations that may arise following prophylaxis on the efficacy of subsequent therapy.

OBJECTIVE - C:

Develop strategies to evaluate, prevent, and treat complications and toxicities of antiretroviral treatment in domestic and international settings.

STRATEGIES:

- Evaluate potential delayed or late effects of ART following short-term administration of prophylaxis regimens, as well as during chronic treatment.
- Support research on the pathogenesis and mechanisms of toxicity of drugs used to treat HIV disease.
- Develop and test approaches to prevent or reverse potential metabolic abnormalities (e.g., changes in body composition, development of atherogenicity and endocrine disorders, and changes in bone and muscle structure) based on an understanding of the mechanisms by which ART and/or suppression of HIV replication may affect metabolic processes.
- Integrate metabolic, endocrine, cardiovascular, neurologic, renal, and bone studies into ongoing and planned treatment trials, including structured treatment interruption studies, which may provide an opportunity to answer important questions related to potential complications of ART.
- Develop approaches to monitor and evaluate the effects of gender, race, and age on complications of ART.
- Evaluate the impact of nutritional deficits, impaired access to safe drinking water, regionally significant co-infections, and other population- and area-specific factors on complications of ART in developing countries.
- Support research on the interactions of antiretroviral treatment on co-infections.
- Evaluate drug interactions with potential clinical significance for HIV-infected individuals, particularly the interactions between ARVs and psychotropic medications; develop strategies to avoid or minimize the clinical impact of these interactions.

OBJECTIVE - D:

Develop and evaluate new agents and strategies for preventing and treating HIV-associated infections and co-infections including diseases unique to or prevalent in international settings.

STRATEGIES:

Preclinical Discovery and Development

- Identify and validate potential molecular targets for the discovery and development of agents for prevention and treatment of HIV-associated infections. Delineate the structure and function of potential molecular targets of HIV-associated opportunistic infections (OIs) and co-infections.
- Support preclinical drug design and development programs to develop therapies against associated pathogens, especially *Pneumocystis*, *Cryptosporidium*, *Mycobacterium avium* complex (MAC), *Mycobacterium tuberculosis*, *Candida*, microsporidia, JC virus (JCV, the etiologic agent of progressive multifocal leukoencephalopathy [PML]), cytomegalovirus (CMV), HPV, HHV-8, azole-resistant fungi, and other prominent co-infections such as hepatitis B and hepatitis C, with emphasis on innovative approaches and agents with favorable bioavailability and pharmacokinetics and development of formulations appropriate for use in children.
- Support and encourage mechanism-based screening of novel synthetic compounds and natural products to identify candidate agents for treating OIs and co-infections; provide support for medicinal chemistry, structural databases, resynthesis, and toxicity testing.
- Cooperate with the private sector to increase involvement and investment in anti-OI and anti-coinfection drug discovery and development research, especially in areas where public health needs are substantial; assume full responsibility, when necessary, for the development of potential therapies with high public health relevance and need.

Clinical Trials of Therapeutic Regimens

- Assess the impact of new antiretroviral regimens on the risks for and manifestations of infections associated with HIV/AIDS in adults, adolescents, and children.
- Improve our understanding of the interplay between HIV-associated immune deficiencies and the onset and types of infectious complications.

- Support clinical research in the context of drug abuse treatment to reduce HIV-associated infections among HIV-infected drug users.

Clinical Trial Methodology

- Improve strategies for prevention of multiple infections in the context of antiretroviral treatment; determine the optimal timing for initiating/discontinuing prophylaxis for different OIs and co-infections; develop improved strategies to minimize toxicities and the development of drug-resistant microorganisms.
- Develop tools to identify HIV-infected individuals at high risk for development of specific OIs and co-infections, to improve the efficiency of clinical trial design and the risk/benefit ratio of the currently utilized drugs for prophylaxis and for treatment.
- Develop clinically useful assays and methodologies for early and rapid diagnosis of OIs and co-infections, quantitative assessment of microbiological responses, and drug sensitivity testing.

Co-infections

- Study the interaction between HIV infection and infectious complications upon pathogenesis, presentation, and disease outcomes in adults, adolescents, and children.
- Support clinical trials, domestic and international, of individuals co-infected with HIV and TB (both active and latent infection). Evaluate safety and efficacy of treatment regimens in co-infected individuals. Determine optimal length of treatment. Evaluate regimens in the context of degree of immunosuppression (late versus middle versus advanced HIV disease).
- Investigate surrogate markers of TB disease that could distinguish between latent, active, and eradicated infection in co-infected individuals; determine how each infection influences or alters the other disease in respect to progression and response to therapy.
- Support clinical trials investigating the efficacy and risks of treatment of hepatitis C in individuals who are co-infected with HIV and HCV; determine how each infection influences or alters the other disease in respect to progression and response to therapy.

- Study the interaction of co-infections with HIV transmission (e.g., placental malaria and perinatal infection) and effects on HIV disease progression.

Pharmacology and Toxicology

- Conduct preclinical studies of anti-OI and anti-coinfection drugs (alone or in partnership with industry) to assess their immunologic, pharmacokinetic, pharmacodynamic, toxic, reproductive, and teratogenic effects, as well as transplacental carcinogenicity.
- Support clinical studies to evaluate the safety and pharmacokinetics of existing and experimental agents intended to treat or prevent OIs and co-infections in HIV-infected infants, children, and pregnant women.
- Evaluate drug interactions between anti-TB agents and HIV medications. Support the investigation of new anti-TB agents with fewer side effects, drug interactions, and/or action against multiple drug-resistant TB (MDR-TB).

Adherence

- Support research on the effectiveness of pharmacologic and other approaches in promoting adherence to anti-coinfection regimens.
- Develop formulations, routes of administration, and delivery systems for existing and experimental anti-OI and anti-coinfection drugs appropriate for use in infants, children, and other populations.
- Develop and evaluate interventions to facilitate better adherence to therapies among populations with HIV infection and substance abuse and/or mental illness.

International

- Conduct clinical trials to evaluate agents for the prophylaxis and treatment of HIV-associated OIs and co-infections; target infections shown to cause significant morbidity by epidemiologic studies, and made worse by HIV-induced immunosuppression.
- Develop and evaluate strategies for treatment and prevention of prevalent opportunistic and endemic infections in the context of HIV infection.

OBJECTIVE - E:

Develop, evaluate, and implement strategies for interrupting mother-to-child transmission (MTCT) applicable to resource-rich and -poor countries, including strategies to interrupt transmission through breastfeeding and evaluation of short- and long-term effects of these interventions on women and infants.

(The scientific objectives of E, F, and G are of equal weight.)

STRATEGIES:

Mechanisms of Transmission

- Investigate the mechanisms and timing of MTCT (*in utero*, intrapartum, and postpartum via breast milk) to facilitate and develop targeted drugs/strategies to further decrease MTCT or provide alternatives to currently identified effective strategies.
- Investigate risk factors associated with early and late breast milk HIV transmission (e.g., breast milk viral load, immune factors, mastitis, and exclusive versus mixed breastfeeding).
- Develop reproducible, sensitive, and specific assays to detect and quantitate the amount of cell-free and cell-associated virus in breast milk.

Interventions and Trials to Evaluate Interventions to Reduce Transmission

- Use and/or develop suitable animal models to evaluate novel strategies to prevent transplacental and postpartum breastfeeding transmission of HIV, and to evaluate transplacental passage of antiretroviral agents and their effects on placental function and on fetal development and viability.
- Develop safe and conveniently administered strategies to interrupt MTCT using interventions that are affordable in resource-poor nations, including specific strategies to prevent postnatal transmission of HIV through breast milk by providing prophylaxis to the infant, mother, or both during the lactational period.
- Evaluate strategies for reducing MTCT when maternal antepartum and intrapartum ART is not given or available (e.g., postpartum prophylaxis of the infant only).
- Support international collaborative efforts to conduct clinical trials of interventions to interrupt MTCT.

- Develop and evaluate strategies for reducing the risk of vertical transmission of HIV from pregnant women to their offspring, and evaluate the impact of that intervention on maternal health treatment options; such strategies may include antiviral agents, anti-HIV immunoglobulin, monoclonal antibodies, agents targeted to cellular targets (e.g., blocking cytokine receptors), cell- and gene-based strategies, vitamin supplementation, HIV vaccines, adjuvants, and virucides, alone or in combination.
- Study the effects of antiretroviral regimens used for maternal health indications on the risk of vertical transmission (including postnatal transmission through breast milk).
- Further evaluate the risks and benefits of cesarean delivery for reducing transmission (e.g., evaluate the risk of postpartum morbidity in infected women with elective cesarean delivery and determine whether the additional benefit of cesarean delivery for preventing transmission accrues in women receiving ART).
- Support research and development of new clinical trial designs, statistical methodologies and investigation of biologic markers, surrogates, and/or other outcomes to evaluate the activity, clinical efficacy, or reasons for failure of new agents and approaches in the treatment of HIV-infected pregnant women and their offspring.
- Develop, incorporate, and validate appropriate quality-of-life parameters and methods to measure antiretroviral drug adherence in clinical trials of HIV-infected pregnant women.

Issues Related to Antiretroviral Drug Resistance

- Evaluate the influence of pre-existing viral drug resistance in pregnant women on the efficacy change to effectiveness of antiretroviral regimens to prevent MTCT.
- Evaluate the risk for the development of HIV variants with detectable antiretroviral drug resistance in pregnant women who receive different types of antiretroviral prophylactic regimens, the kinetics and durability of such resistance in cell-free and cell-associated virus, and the effects of the development of such resistance on maternal health and response to future therapy.

- Evaluate the risk for development of HIV variants with detectable antiretroviral drug resistance in infants who become infected despite maternal receipt of antiretroviral prophylaxis regimens, the kinetics and durability of such resistance in cell-free and cell-associated virus, and the effects of such resistance on infant health and response to future therapy.
- Evaluate the effect of drug resistance developing following antiretroviral prophylaxis in an initial pregnancy on the efficacy of the prophylactic regimen in reducing transmission in subsequent pregnancies.
- Develop and evaluate interventions capable of reducing the risk for developing antiretroviral drug-resistant virus in women receiving antiretroviral prophylactic regimens.

Issues Related to Short- and Long-Term Effects of Antiretroviral Prophylaxis for Reducing Transmission on Women and Children

- Evaluate the toxicities, pharmacokinetics (including transplacental drug transfer to fetus/infant), and antiretroviral activity of new agents, existing agents, and combinations of agents in pregnant HIV-infected women and their neonates.
- Evaluate the potential mechanism for possible carcinogenic or mutagenic effects of *in utero* antiretroviral exposure.
- Study the effects of antiretroviral regimens used during pregnancy for treatment of maternal HIV disease (as opposed to use only to prevent perinatal transmission) on maternal health and pregnancy outcome.
- Evaluate the short- and long-term clinical, immunologic, and virologic effects of receiving ART during pregnancy for the sole purpose of preventing perinatal transmission in women who choose to discontinue antiretroviral treatment after delivery.
- Evaluate the short- and long-term clinical, immunologic, and virologic effects in women receiving ART during lactation, solely to prevent breast milk transmission, but who discontinue treatment following weaning.
- Support the long-term followup of children exposed to ARVs during pregnancy and/or postpartum to evaluate possible late effects of such exposure.

Implementation Issues

- Develop and evaluate strategies for implementation of effective perinatal transmission prevention interventions in resource-poor and -rich countries, including ways to increase availability and acceptability of prenatal HIV testing and of prophylaxis to prevent MTCT.
- Improve the sensitivity and specificity of diagnostic procedures that are accessible, cost-effective, and have utility in resource-poor and -rich settings to permit the earliest possible determination of HIV infection in infants, and whether antiretroviral and/or immunopreventive therapies affect the timing and sensitivity of these assays for diagnosis.
- Evaluate innovative methods, including rapid HIV antibody testing, to identify HIV infection in pregnant women with unknown HIV serostatus who present in labor and to assess the acceptability of such testing and acceptability and efficacy of antiretroviral prophylaxis to reduce MTCT, when administered to the woman intrapartum and her infant, or to her infant alone.
- Evaluate the public health impact of programs to prevent MTCT.

OBJECTIVE - F:

Evaluate the impact of antiretroviral and immunotherapeutic strategies and their roles in the prevention of horizontal HIV transmission (e.g., sexual or IDU transmission) in appropriate domestic and international settings.

(The scientific objectives of E, F, and G are of equal weight.)

STRATEGIES:

Mechanisms of Transmission

- Evaluate the influence of drug resistance on the efficacy of antiretroviral regimens to prevent sexual transmission.
- Use and/or develop suitable animal models to evaluate genital and anal passage of ARVs.

Interventions to Reduce Transmission

- Support international collaborative efforts to conduct trials of antiretroviral, immunotherapeutic, and other treatment interventions with an endpoint of sexual transmission.
- Develop and evaluate strategies for reducing the risk of sexual transmission of HIV without compromising treatment of the HIV-infected individual; such strategies may include antiviral agents, therapeutic vaccines, anti-HIV immunoglobulin, monoclonal antibodies, and microbicides, alone or in combination.

Issues Related to Antiretroviral Interventions

- Evaluate the risk for development of antiretroviral drug resistance (in cell-free and cell-associated virus, and in sequestered genital or anorectal sites) when using ARVs in interventions to reduce horizontal transmission, including the development of antiretroviral drug resistance in individuals who become HIV-infected while receiving such therapy or in HIV-infected individuals being administered such therapy solely to reduce horizontal transmission.
- Evaluate the public health impact of regimens to reduce viral load on sexual transmission.
- Evaluate the public health impact of treatment interruptions on HIV transmission.

OBJECTIVE - G:

Develop and evaluate therapeutic approaches, including therapeutic vaccine candidates, that will restore and sustain a competent immune system in HIV-infected individuals.

(The scientific objectives of E, F, and G are of equal weight.)

STRATEGIES:

- Employ approaches to enhance immune restoration in clinical trials; test specific hypotheses of HIV immunopathogenesis.
- Evaluate the capacity of the immune system to maintain or repair itself after maximal effective viral suppression.
- Evaluate immune-based therapies for the purpose of improving ART-sparing regimens, permitting delay in initiating or reinitiating ART in regimens of scheduled intermittent therapy (SIT).
- Develop, validate, and standardize new methods for evaluating immune function in clinical trials that enroll adults, adolescents, and children, including assays that may be used in resource-poor settings.
- Accelerate the preclinical and clinical testing of cytokines, modulators of cytokines, and immunoactive agents to prevent further immune deterioration, to reconstitute deficient immune systems, and to enhance the immunogenicity of therapeutic HIV vaccines.
- Develop and evaluate active and passive immunotherapeutic approaches for HIV infection and its sequelae, including the testing of optimum immunogens; determine best patient disease status for response, most effective immunization dose and schedule, and most meaningful read-out of clinical impact of the intervention.
- Support research on approaches to facilitate better adherence to immunoactive regimens.
- Evaluate the safety and efficacy of administering cellular immune elements, including use of expanded peripheral blood T cells, bone marrow, cord blood stem cell transplantation, and thymic transplantation.
- Evaluate the immune system after partial restoration by effective ART. Define qualitative and quantitative differences between the restored immune system and the naive immune system to determine if identified deficiencies can be diminished by immunoactive agents including the use of vaccines for specific OIs.

- Develop new therapeutic strategies based on gene delivery strategies to protect mature, hematopoietic stem cells, hematopoietic pluripotent cells, and stromal cell elements from destruction by HIV.
- Evaluate the potential to inhibit HIV replication and spread by modifying chemokine receptor expression and/or chemokine levels. Develop agents to block the attachment of HIV to receptors and co-receptors and thus inhibit entry into cells.
- Study the mechanisms of action of immunomodulating agents, and proceed with applied studies and development of the most promising approaches.
- Evaluate immunologic markers that may identify individuals at risk for late complications of therapy.
- Develop standards and definitions to allow better comparisons of late complications across clinical trials.
- Evaluate treatment interruption both to stimulate HIV-specific immune responses (structured treatment interruption [STI]) and as an analytic read-out of treatment effects (analytic treatment interruption [ATI]).
- Evaluate immune-based therapy as an adjunct to salvage therapy strategies.

	<p>OBJECTIVE - H:</p> <p>Develop strategies for assessing, preventing, and treating HIV nervous system infection and central and peripheral nervous system manifestations of HIV disease.</p> <p>(The scientific objectives of H, I, and J are of equal weight.)</p>
<p>STRATEGIES:</p>	<ul style="list-style-type: none"> • Develop and evaluate novel strategies and agents, such as neuroprotective agents, that are active against putative pathways of HIV-induced CNS dysfunction in adults, adolescents, and children. • Develop and utilize <i>in vitro</i> and animal models of CNS lentivirus infections and CNS injury to identify therapeutic agents for the nervous system complications of HIV infection. • Assess the pathogenic role of viral sequestration in the CNS, including its potential role as a reservoir of viral persistence and as a site of independent selection of antiviral drug-resistant strains and other mutants. • Design and conduct clinical trials addressing nervous system complications of HIV infection in adults, adolescents, and children. • Determine the incidence and prevalence of HIV-associated neurologic disease after long-term ART. • Develop objective quantitative assessments (e.g., surrogate markers in cerebrospinal fluid [CSF] and neuroimaging) of treatment effects. • Develop therapeutic agents to block HIV entry into the CNS and treat HIV infection in the CNS; evaluate their safety and efficacy in clinical trials. • Characterize the CNS pharmacokinetics and pharmacodynamics of ARVs; determine the importance of CNS drug penetration, particularly penetration of the blood-brain barrier, in reducing CNS infection in neurologically symptomatic and asymptomatic subjects. • Develop strategies for manipulating drug transporters at the blood-brain barrier to facilitate entry of ARVs into the CNS compartment. • Develop better strategies including complementary and alternative medicine therapies to prevent, diagnose, and treat peripheral neuropathies in HIV-infected individuals.

- Conduct studies to determine drug interactions between commonly used treatments for HIV disease and its complications, with treatments for drug abuse and co-occurring mental health disorders.
- Validate and enhance the efficiency of neuropsychological and neurologic tests performed in the context of clinical trials to identify those tests most capable of determining treatment-related changes in different age and racial/ethnic groups.
- Determine the prevalence, causes, and pathogenesis of pain in HIV-infected individuals and develop optimal therapies for pain management.
- Monitor CSF for HIV viral load and immune activation markers in individuals enrolled in studies of ART.
- Further elucidate the correlation among CSF HIV viral load, chemokine levels, proinflammatory cytokines, and markers of immune activation with CNS disease in clinical trials.
- Support the research and development of new statistical methodologies, clinical trial designs, and selection and investigation of biologic markers, to evaluate the safety and clinical efficacy of new agents and approaches in the treatment of neurologic complications of HIV disease.
- Support research on the effectiveness of pharmacologic and other approaches to facilitate better adherence to therapeutic regimens in neurologically impaired individuals.
- Evaluate the effectiveness of reducing HIV-associated CNS disease burden by therapeutic agents currently used to treat other neurologic diseases (e.g., Parkinson's and Alzheimer's disease) that may share pathophysiologic features with HIV-associated neurologic disease.
- Develop, incorporate, and validate functional neurologic and quality-of-life scales that are aimed at measuring the impact of nervous system complications of HIV infection in clinical trials.
- Selectively incorporate neurologic and neuropsychological assessments into HIV-related clinical trials.

	<p>OBJECTIVE - I:</p> <p>Discover, develop, and evaluate improved strategies for the assessment, treatment, and prevention of cancer-specific manifestations of HIV disease.</p> <p>(The scientific objectives of H, I, and J are of equal weight.)</p>
<p>STRATEGIES:</p>	<p>Pathogenesis Research and Preclinical Drug Development</p> <ul style="list-style-type: none"> • Identify novel mechanisms and targets (e.g., cytokines, angiogenesis factors, and hormones) for treatment and prevention of HIV-associated tumors such as Kaposi's sarcoma (KS), non-Hodgkin's lymphoma (NHL), and HPV malignancies, including anogenital dysplasias and cancers; develop new therapeutic strategies based on these findings. • Develop <i>in vitro</i> models of KS and assays for angiogenesis inhibitors. • Promote screening, discovery, and development of novel therapeutic agents with activity against HIV-associated malignancies, including pathogenesis-based strategies, agents with better CNS penetration, and agents with better safety profiles. • Based upon structural biologic and biochemical information, develop therapeutic agents for the treatment of HIV-associated malignancies. • Develop preclinical and <i>in vivo</i> models (e.g., severe combined immunodeficiency-human [SCID-hu] mice) for the testing of potential therapeutic strategies against HIV-associated malignancies. <p>Diagnostic Methods</p> <ul style="list-style-type: none"> • Improve methods for early diagnosis of malignancies and for early detection of recurrent cancer. <p>Clinical Evaluation of Therapeutic and Prevention Strategies</p> <ul style="list-style-type: none"> • Develop therapeutic and prevention strategies for HIV-associated malignancies based on an improved understanding of the role of infectious agents (e.g., Kaposi's sarcoma-associated herpesvirus [KSHV]/HHV-8, Epstein-Barr virus [EBV], HPV, and HBV) in their pathogenesis.

- Evaluate novel approaches for the treatment of HIV-associated malignancies through clinical trials, and evaluate the interactions between treatment of malignancies and treatment of the underlying HIV infection.
- Support approaches using gene-based technologies, such as tissue array and microarray in targeting treatment of HIV-associated malignancies.
- Develop, incorporate, and validate clinical trial methodologies to correlate tumor-specific responses with clinical benefit, including quality-of-life parameters; develop a staging system indicative of prognostic response and survival.
- Encourage collaborative studies within clinical trials networks to develop mechanisms for early identification of individuals at high risk for malignancies. Develop and assess interventional strategies to reduce the risk or prevent the development of malignancies.
- Study the role of immunomodulating agents in the treatment and prevention of AIDS-related tumors.
- Encourage clinical studies of HIV-infected individuals with non-AIDS-defining malignancies. Evaluate the impact of therapy upon virologic, immunologic, tumor parameters, and drug-drug interactions.
- Explore strategies for attenuating or preventing toxicities associated with therapy, and study the effects of such strategies on virologic and immunologic parameters.
- Study the role of *in utero* exposure to ARVs on the risk of later development of tumors, in both uninfected and infected children born to HIV-infected women who received ARVs during pregnancy.
- Study populations in resource-poor settings at increased risk of AIDS-related malignancies due to endemic infectious agents (e.g., HHV-8) and HPV-associated cervical cancer in women.

OBJECTIVE - J:

Develop and evaluate strategies for the treatment and prevention of serious organ-specific manifestations of HIV disease including those prevalent in or unique to international settings.

(The scientific objectives of H, I, and J are of equal weight.)

STRATEGIES:

- Develop and evaluate therapeutic strategies for preventing and treating complications of HIV infection, particularly those complications unique to or prevalent in international settings.
- Develop and evaluate conventional and nonconventional chemopreventive approaches, including those containing quantifiable doses of micronutrients (such as vitamins and trace elements) and macronutrients to delay the development of wasting and other complications of HIV disease.
- Evaluate the safety and efficacy of complementary and alternative medicine therapies, including nonpharmacologic interventions such as exercise, nutrition, and sleep cycles, in the management of HIV disease and its complications.

APPENDIX A:

NIH Institutes and Centers

NIH INSTITUTES AND CENTERS

NCI	National Cancer Institute
NEI	National Eye Institute
NHLBI	National Heart, Lung, and Blood Institute
NHGRI	National Human Genome Research Institute
NIA	National Institute on Aging
NIAAA	National Institute on Alcohol Abuse and Alcoholism
NIAID	National Institute of Allergy and Infectious Diseases
NIAMS	National Institute of Arthritis and Musculoskeletal and Skin Diseases
NIBIB	National Institute of Biomedical Imaging and Bioengineering
NICHD	National Institute of Child Health and Human Development
NIDCD	National Institute on Deafness and Other Communication Disorders
NIDCR	National Institute of Dental and Craniofacial Research
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NINDS	National Institute of Neurological Disorders and Stroke
NIDA	National Institute on Drug Abuse
NIEHS	National Institute of Environmental Health Sciences
NIGMS	National Institute of General Medical Sciences
NIMH	National Institute of Mental Health
NINR	National Institute of Nursing Research
NLM	National Library of Medicine
CC	Warren Grant Magnuson Clinical Center
CIT	Center for Information Technology
NCCAM	National Center for Complementary and Alternative Medicine
NCRR	National Center for Research Resources
FIC	John E. Fogarty International Center
CSR	Center for Scientific Review
NCMHD	National Center on Minority Health and Health Disparities

APPENDIX B:

FY 2005 OAR
Planning Group for
Therapeutics

FY 2005 THERAPEUTICS PLANNING GROUP

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APPENDIX C:

List of Acronyms

LIST OF ACRONYMS

ACSR	AIDS and Cancer Specimen Resource, NCI
ACTIS	AIDS Clinical Trials Information Service
AIDS	acquired immunodeficiency syndrome
AITRP	AIDS International Training and Research Program, FIC
ART	antiretroviral therapy
ARV	antiretroviral
ATI	analytic treatment interruption
ATIS	AIDS Treatment Information Service
AVEG	AIDS Vaccine Evaluation Group
BSL	biosafety level
B/START	Behavioral Science Track Award for Rapid Transition
CAB	community advisory board
CAPS	Center for AIDS Prevention Studies (University of California, San Francisco)
CBO	community-based organization
CDC	Centers for Disease Control and Prevention
CIPRA	Comprehensive International Programs for Research on AIDS
CMV	cytomegalovirus
CNS	central nervous system
CSF	cerebrospinal fluid
CTL	cytotoxic T lymphocyte
DC	dendritic cell
DHHS	Department of Health and Human Services
EBV	Epstein-Barr virus
FDA	Food and Drug Administration
GBV-C	GB virus (hepatitis G)
GCP	Good Clinical Practices
GCRC	General Clinical Research Center
GFATM	Global Fund for AIDS, Tuberculosis, and Malaria

GI	gastrointestinal
GLP/GMP	good laboratory practice/good manufacturing practice
GRIP	Global Health Research Initiative Program, FIC
HAART	highly active antiretroviral therapy
HBCU	Historically Black Colleges and Universities
HBV	hepatitis B virus
HCV	hepatitis C virus
HHV	human herpesvirus
HIV	human immunodeficiency virus
HPV	human papillomavirus
HSV	herpes simplex virus
HVTN	HIV Vaccine Trials Network
IC	Institute and Center
ICC	invasive cervical cancer
IDU	injecting drug user
IND	investigational new drug
IRB	institutional review board
IUD	intrauterine device
JCV	JC virus
KS	Kaposi's sarcoma
KSHV	Kaposi's sarcoma herpesvirus
LRP	Loan Repayment Program, NIH
MAb	monoclonal antibody
MAC	<i>Mycobacterium avium</i> complex
MDR-TB	multidrug-resistant tuberculosis
MHC	major histocompatibility complex
MSM	men who have sex with men
MTCT	mother-to-child transmission
NAFEO	National Association for Equal Opportunity in Higher Education
NGO	nongovernment organization

NHL	non-Hodgkin's lymphoma
NHP	nonhuman primate
NIH	National Institutes of Health
NK	natural killer (cell)
NMAC	National Minority AIDS Council
NNTC	National NeuroAIDS Tissue Consortium, NIMH/NIDA/NINDS
NRTIs	nucleoside reverse transcriptase inhibitors
OAR	Office of AIDS Research, NIH
OARAC	Office of AIDS Research Advisory Council
OD	Office of the Director, NIH
OI	opportunistic infection
PACTG	Pediatric AIDS Clinical Trials Group
PCP	<i>Pneumocystis carinii</i> pneumonia
PML	progressive multifocal leukoencephalopathy
RCT	randomized clinical trial, randomized controlled trial
RNA	ribonucleic acid
RPRC	Regional Primate Research Center
SCID	severe combined immunodeficiency
SHIV	chimeric simian/human immunodeficiency virus
SIT	scheduled intermittent therapy
SIV	simian immunodeficiency virus
SPF	specific pathogen-free
STD	sexually transmitted disease
STI	structured treatment interruption; sexually transmitted infection
TB	tuberculosis
UNAIDS	Joint United Nations Programme on HIV/AIDS
USAID	U.S. Agency for International Development
VRC	Vaccine Research Center
WHO	World Health Organization
WIHS	Women's Interagency HIV Study
WRAIR	Walter Reed Army Institute of Research

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